

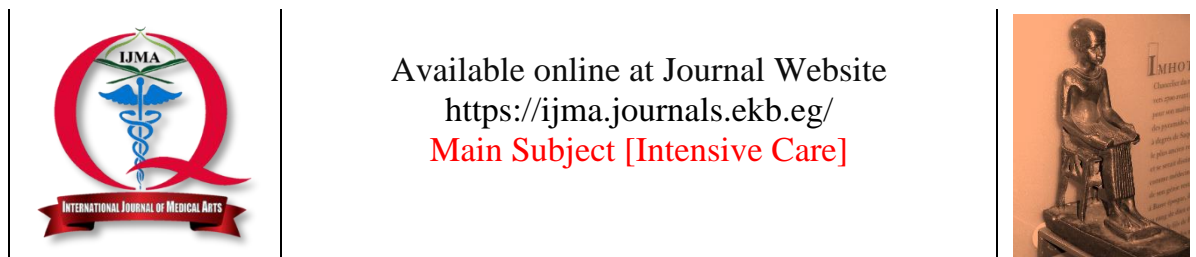
IJMA



INTERNATIONAL JOURNAL OF MEDICAL ARTS

VOLUME 6, ISSUE 6, JUNE 2024

P- ISSN: 2636-4174
E- ISSN: 2682-3780



Original Article

Comparative Study between Different Levels of Positive End - Expiratory Pressure in non- Acute Respiratory Distress Intensive Care Unit Patients

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ABSTRACT

Article information

Received: 29-08-2022

Accepted: 11-06-2023

DOI:
10.21608/IJMA.2023.159435.1504.

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Citation: Eldabour MSM, Abdelsalam YM, Elkassas MHM, Harby SA. Comparative Study between Different Levels of Positive End - Expiratory Pressure in non- Acute Respiratory Distress Intensive Care Unit Patients. IJMA 2024 June; 6 [6]: 4612-4619. doi: 10.21608/IJMA.2023.159435.1504.

Background: Positive end-expiratory pressure [PEEP] is commonly used in mechanically ventilated patients to prevent alveolar collapse and improve oxygenation. However, optimal PEEP levels remain controversial, especially in non-acute respiratory distress syndrome patients in the intensive care unit [ICU].

The aim of the work: To compare the effects of different PEEP levels on oxygenation status and clinical outcomes in non-acute respiratory distress ICU patients requiring invasive mechanical ventilation.

Patients and Methods: This prospective randomized controlled trial included 80 ICU patients without acute respiratory distress syndrome who required invasive mechanical ventilation. Patients were randomized to receive low [4-8 cmH₂O] or high [9-12 cmH₂O] PEEP levels. The primary outcomes were Pao₂ to Fio₂ ratio, as an indicator for improvement of oxygenation parameter and number of ventilator-free days at day seven.

Results: The Fio₂ values for the 4 to 8 cm H₂O group averaged 0.42 [±0.19] and differed significantly from the 9 to 12 cm H₂O group, which averaged 0.40 [±0.22] [p < 0.001]. However, no significant differences were found in respiratory rates, heart rates, mean arterial pressures, ARDS, severe hypoxemia, or ICU and hospital mortality. Driving pressures significantly differed [14.75 ± 1.56 vs. 12.5 ± 1.2; p < 0.001]. Ventilator-free days were similar, averaging 2.92 [±1.46] and 4.0 [±0.93] [p=0.056].

Conclusion: Ventilation with different levels of PEEP in ICU patients without ARDS at the onset of ventilation was associated with higher Po₂/ Fio₂ but not associated with decrease in ventilator free days nor lower in-hospital mortality nor a lower incidence of ARDS or pneumonia.

Keywords: Acute Respiratory Distress; Intensive Care Unit; Expiratory Pressure; Hemodynamic.



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INTRODUCTION

While invasive ventilation is one of the most commonly utilized strategies in the intensive care unit [ICU], it remains a potentially harmful intervention. The role of low tidal volume is well-known; however, it is still uncertain if higher positive end-expiratory pressure [PEEP] can be effective [1].

In ICUs all over the world, there has been a steady rise in the use of increased PEEP in patients without ARDS. Recently, it was shown that PEEP increased from a mean of 5 cm H₂O in 1998 to 7 cm H₂O in 2016 [2]. Of note; there has been a worldwide mounting increase in the use of higher PEEP in subjects without ARDS in ICUs [3].

In patients without ARDS, ventilation through higher PEEP could enhance lung aeration, which improves oxygenation [3]. It was demonstrated that higher PEEP ventilation during surgical procedures worsened vital data and increased the requirement for extra fluid supply and vasopressors [4], also it is typical to extubate at a lower PEEP level [5].

Acute respiratory distress syndrome [ARDS] is an acute illness that begins seven days after the initial trigger and is characterized by bilateral pulmonary infiltrates and severe progressive hypoxia in the absence of cardiogenic pulmonary edema. A PaO₂/FiO₂ ratio of less than 300 indicates the presence of ARDS, which is determined by the patient's arterial blood oxygen saturation [PaO₂] to the percentage of inspired oxygen [FiO₂] [6].

The main aim of this study was to compare different levels of Positive End-Expiratory Pressure among patients with non-ARDS respiratory causes regarding the improvement of oxygenation parameter, survival rate and mortality rate within 7 days, hemodynamic parameters and developed complications including the development of ARDS, severe hypoxemia, and pneumothorax and the need for inotropic support.

PATIENTS AND METHODS

A prospective comparative randomized clinical trial comparing different levels of PEEP among mechanically ventilated patients due to respiratory causes other than ARDS.

Inclusion criteria: This study was carried out at the Faculty of Medicine, Al-Azhar University; Damietta, Egypt on Patients admitted to the Intensive Care Units [ICUs] due to causes other

than ARDS and need for invasive ventilation and patients above 21 years old [adult].

Exclusion criteria: Patients on MV due to respiratory failure of severe chronic obstructive pulmonary disease [COPD] cause, patients with ongoing cardiac ischemia, patients with increased intra-cranial tension, patients with suspected or confirmed pregnancy, and any neurologic disorder that may extend the period of ventilation, e.g., Guillain–Barré syndrome, upper spinal cord injury or multiple sclerosis.

End point: Seven days of ventilation or accomplishment of successful weaning of the patient.

Sample size: The sample size was calculated using MedCalc® version 12.3.0.0 statistical software from Ostend, Belgium, employing a 95% confidence interval and a study power of 90% with an α error of 5%. According to the formula, a minimum of 70 patients was necessary to detect a significant difference at an α level of 0.05, based on the assumptions derived from previous research [7]. To further enhance the statistical power of our study, we included a total of 80 participants.

Patients: Eighty patients who underwent invasive ventilation after being admitted to the ICU for a respiratory condition other than ARDS and who weren't anticipated to be extubated within 24 hours of randomization were included in the study. Patients were randomly assigned within an hour of the ICU's starting ventilation.

Randomization and Masking: Patients were randomized after approval of the ethics committee in a 1:1 ratio to a PEEP strategy group first group received PEEP from [8 to 4 cm H₂O] the 2nd group received PEEP from [12 to 9 cm H₂O].

Examinations: vital signs including Glasgow Coma Scale [GCS], blood pressure [BP], respiratory rate [RR], heart rate, temperature and O₂ saturation, and chest and cardiac examination.

Laboratory investigations: Arterial blood gases: PH, PO₂, PCO₂, HCO₃, complete blood count: Hemoglobin, Platelets and White Blood Cells, serum Electrolytes: Sodium, Potassium, serum Creatinine, SGOT, SGPT, CRP, ESR.

Interventions: Patients were randomly assigned in a 1:1 ratio to one of two PEEP strategy groups. The first group received PEEP between 4 and 8 cm H₂O, while the second group received PEEP

between 9 and 12 cm H₂O, as well as an inspired oxygen fraction [FiO₂] ranging from 0.35 to 0.8. PEEP was reduced by 1 cm H₂O every 15 minutes after intubation and the start of ventilation, as long as the oxygen saturation [Spo₂] assessed by pulse oximetry is greater than 92% or the Pao₂ is greater than 60 mm Hg. The lowest FiO₂ of between 0.35 and 0.8 is used in ventilation while maintaining the lowest PEEP in accordance with this aim. Spo₂. For brief intervals [up to 5 minutes], spo₂ was permitted to drop to the desired level without any interference. Then, FiO₂ was raised to a maximum of 0.8 before the gradual induction of PEEP. When the Pao₂ or Spo₂ drops to less than 88% or less than 55 mmHg, it is said to have severe hypoxemia. FiO₂ may be elevated to a maximum of 1.0 as a last resort.

Oxygenation Targets: Spo₂ and Pao₂ oxygenation goals for all groups ranged from 92% to 96% and 60 to 100 mm Hg, respectively [8, 9]. An arterial blood gas study was used to determine the oxygenation goal and follow up by pulse oximetry.

Standard ventilator management: All ventilator modes are permitted as long as they do not automatically modify PEEP and FiO₂. The most popular ventilator modes are volume-controlled ventilation, pressure-controlled ventilation, and pressure support ventilation. The respiratory rate was modified to achieve a normal arterial blood pH [7.35 to 7.45], and the tidal volume size is between 6 and 8 ml/kg projected body weight [PBW]. Driving pressure was measured as [Plateau pressure - Total PEEP] and was used as the main factor to control ventilation and we kept driving pressure below 14 cm H₂O. The Patient was undergoing MV via Drager Evita 4 ventilators, monitored by Intellivue MX800 Philips monitors.

Weaning from ventilation: Every six hours, clinicians and assistance nurses check to see if the patient activates the vein to convert to an assisted mode. The decision to extubate a patient is made by the attending physicians based on general extubating criteria, which include adequate patient adaptability and interaction, an appropriate cough reflex, oxygenation saturation > 90% with PaO₂ to FiO₂ ratio > 200 mmHg at FiO₂ 0.4, and respiratory rate between 8 and 30 breaths per minute without any indications of respiratory distress, such as pronounced accessory muscle use, abdominal paradox, diaphoresis, or dyspnea. Low PEEP patients were extubated and weaned while using the lowest PEEP. Patients who were given high PEEP were weaned and extubated at 8 cm H₂O PEEP.

Primary Outcomes

1. [Pao₂ to FiO₂ ratio] as an indicator for improvement of oxygenation parameter.

2. Number of ventilator-free days at day 7, defined as the number of days that a patient was alive and free of invasive ventilation, calculated from the moment of randomization if the period of unassisted breathing lasted at least 24 consecutive hours. Patient who died or received invasive ventilation for more than 7 days were considered to have 0 ventilator-free days.

Secondary Outcomes

- Hemodynamic parameters [respiratory rate, heart rate and blood pressure].

- Any developed complications including development of ARDS, severe hypoxemia, and pneumothorax.

- Survival rate and mortality rate within 7 days and 28 day.

- Number of days with use of vasopressors or sedation

Statistical Analysis: Data were analyzed using SPSS 26.0 for windows [SPSS Inc., Chicago, IL, USA]. The Shapiro–Wilk test was used to test normal distribution. Mean and standard deviation were used as descriptive statistics. Chi-square test was used to analyze categorical variables. Mann-Whitney and student t test were used for numerical variables. P value < 0.05 was considered significant.

RESULTS

There were no significant differences in sex [p=0.816], type of admission [p=0.592], or reason for intubation [p=0.805] between the two PEEP groups. Age ranged from 43 to 85 years in the 4 to 8 cm H₂O PEEP group [mean ± SD = 65.55 ± 13.54] and from 36 to 87 years in the 9 to 12 cm H₂O group [mean ± SD = 66.28 ± 12.73], with no significant difference [p=0.806]. The Lung Injury Prediction Score [LIPS] was slightly higher in the 9 to 12 cm H₂O group [mean ± SD = 3.68 ± 0.92] compared to 3.18 ± 0.87 in the other group, but this was not statistically significant [p=0.055] [Table 1].

The FiO₂ values in the 4 to 8 cm H₂O PEEP group ranged from 0.30 to 0.52 [mean ± SD = 0.42 ± 0.19], while in the 9 to 12 cm H₂O group,

they ranged from 0.28 to 0.45 [mean \pm SD = 0.40 \pm 0.22], showing a significant difference [$p < 0.001$]. The Fio₂/PaO₂ ratio also differed significantly [$p < 0.001$] [Table 2].

The study found no significant differences in respiratory rates, heart rates, or mean arterial pressures between the two PEEP groups. The respiratory rates ranged from 12 to 20 [mean \pm SD = 18.98 \pm 4.49] in the 4 to 8 cm H₂O group and 11 to 20 [mean \pm SD = 18.95 \pm 5.25] in the 9 to 12 cm H₂O group [$p=0.982$]. Heart rates were similar, averaging 94.42 \pm 25.4 and 92.95 \pm 29.39 [$p=0.811$]. Mean arterial pressures also showed no significant difference, with values of 79.8 \pm 18.8 and 81.03 \pm 19.45 [$p=0.775$] [Table 3].

The study found no significant differences between the two groups regarding ARDS [$p=0.314$], severe hypoxemia [$p=0.775$], and pneumothorax [$p=0.556$]. ICU mortality at day 7 showed no difference [$p=0.816$], with 14 deaths in group I and 15 in group II. Hospital mortality at days 7

and 28 was also not significantly different [$p=0.82$], with three deaths recorded in each group by day 28 [Table 4].

Driving pressure in the 4 to 8 cm H₂O PEEP group ranged from 11 to 18, with a mean \pm SD of 14.75 \pm 1.56, while the 9 to 12 cm H₂O PEEP group had driving pressures from 11 to 15, with a mean \pm SD of 12.5 \pm 1.2, showing a significant difference [$p<0.001$]. Ventilator-free days averaged 2.92 \pm 1.46 in the first group and 4 \pm 0.93 in the second, without a significant difference [$p=0.056$] [Table 5].

In the study, the 4 to 8 cm H₂O PEEP group had a mean of 2.65 days [± 0.8] on vasopressors, while the 9 to 12 cm H₂O group had a mean of 2.12 days [± 0.61], showing no significant difference [$p=0.051$]. Regarding sedation, both groups used it for similar durations, with means of 2.3 days [± 0.82] and 2.48 days [± 0.93], respectively [$p=0.376$] [Table 6].

Table [1]: Comparison of demographic and clinical parameters between study groups

		4 to 8 cm H ₂ O PEEP group [n = 40]	9 to 12 cm H ₂ O PEEP group [n = 40]	Test of Sig.	p
Sex, n [%]	Male	26 [65%]	25 [63%]	X ² = 0.054	0.816
	Female	14 [35%]	15 [37%]		
Age [years]	Mean \pm SD	65.55 \pm 13.54	66.28 \pm 12.73	t = -0.247	0.806
	Min. – Max.	43 – 85	36 – 87		
Type of admission, n [%]	Surgical	10 [25%]	8 [20%]	X ² = 0.287	0.592
	Medical	30 [75%]	32 [80%]		
Reason of intubation, n [%]	Respiratory failure	12 [30%]	11 [27.5%]	X ² = 0.061	0.805
	Others	28 [70%]	29 [72.5%]		
LIPS score	Mean \pm SD	3.18 \pm 0.87	3.68 \pm 0.92	t = 2.497	0.055

Table [2]: Oxygenation parameter among the study population

		4 to 8 cm H ₂ O PEEP group [n = 40]	9 to 12 cm H ₂ O PEEP group [n = 40]	Test of Sig.	p
Fio ₂	Mean \pm SD.	0.42 \pm 0.19	0.40 \pm 0.22	t = 0.065	<0.001
Pao ₂ /Fio ₂ [mm Hg]	Mean \pm SD.	225.48 \pm 111	256.1 \pm 115.53	t = -0.655	<0.001

Table [3]: Comparison of hemodynamic parameters between study groups

		4 to 8 cm H ₂ O PEEP group [n = 40]	9 to 12 cm H ₂ O PEEP group [n = 40]	Test	P
Heart rate [b/min]	Mean \pm SD	94.42 \pm 25.4	92.95 \pm 29.39	0.24	0.811
Respiratory rate [cycle/min]	Mean \pm SD	18.98 \pm 4.49	18.95 \pm 5.25	0.023	0.982
Mean arterial pressure [mm Hg]	Mean \pm SD	79.8 \pm 18.8	81.03 \pm 19.45	0.286	0.775

Table [4]: Developed complications and mortality rate among the study population

	4 to 8 cm H2O PEEP group [n = 40]		9 to 12 cm H2O PEEP group [n = 40]		X ²	p
	No.	%	No.	%		
Complications						
ARDS [n, %]	1	2.5%	0	0%	1.013	0.314
Severe hypoxemia [n, %]	8	20%	7	17.5%	0.082	0.775
Pneumothorax	2	5%	1	2.5%	0.346	0.556
Mortality						
Intensive care unit at 7 days	14	35%	15	38%	0.054	0.816
Hospital [ICU +ward] at 7 days	16	40%	17	43%	0.052	0.82
Hospital [ICU +ward] at 28 days	17	43%	18	45%	0.051	0.822

Table [5]: Driving pressure and ventilator free days among the study population

		4 to 8 cm H2O PEEP group [n = 40]		9 to 12 cm H2O PEEP group [n = 40]		Test	p
		Mean ± SD		Mean ± SD			
Driving pressure [cm H2O]	Mean ± SD	14.75 ± 1.56		12.5 ± 1.2		7.22	<0.001
Ventilator free days	Mean ± SD	2.92 ± 1.46		4 ± 0.93		2.546	0.056

Table [6]: Days with continuous use of vasopressors and sedation among the study population

		4 to 8 cm H2O PEEP group [n = 40]		9 to 12 cm H2O PEEP group [n = 40]		Test of Sig.	P
		Mean ± SD.		Mean ± SD.			
Days with continuous use of vasopressors	Mean ± SD.	2.65 ± 0.8		2.12 ± 0.61		t = 3.3	0.051
Days with continuous use of sedation	Mean ± SD.	2.3 ± 0.82		2.48 ± 0.93		t = -0.89	0.376

DISCUSSION

Mechanical ventilation [MV] can save lives in critically ill patients but may also lead to lung injuries known as ventilator-induced lung injury [VILI]. Causes include alveolar over-distension and repetitive opening and closing of airways. PEEP helps prevent alveolar collapse, but excessive PEEP can increase mechanical stress and cause hemodynamic issues ^[10].

PEEP not only enhances lung aeration but also affects heart loading conditions by decreasing preload and potentially altering the right ventricle's afterload based on lung tissue recruitment. Its impact on systemic circulation depends on both recruited lung tissue and lung volume, with increased PEEP likely boosting cardiac output when lung volume is below functional residual capacity ^[11].

The study analyzed oxygenation parameters between two PEEP groups. The 4 to 8 cm H2O PEEP group had a mean Fio2 of 0.42 ± 0.19, while the 9 to 12 cm H2O group had a mean Fio2

of 0.40 ± 0.22 [p=0.001]. Similarly, the Pao2/Fio2 ratio was significantly different, with means of 225.48 ± 111 and 256.1 ± 115.53, respectively [p=0.001].

In a meta-analysis by **Serpa Neto et al.** ^[3] 21 RCTs involving 1,393 patients were included. PEEP levels ranged from 0 to 10 cmH2O in the lower PEEP group and from 5 to 30 cmH2O in the higher PEEP group. Higher PEEP resulted in increased PaO2/FiO2 in five RCTs [SMD 0.72; 95% CI 0.10–1.35; I² = 86%], consistent with our findings. Conversely, another meta-analysis by **Pettenuzzo et al.** ^[12] reviewed 22 RCTs with 2,225 patients, comparing higher PEEP [1,007 patients] to lower PEEP [991 patients]. Among secondary outcomes, higher PEEP showed improved oxygenation, enhancing the PaO2/FiO2 ratio, the A-aDO2 difference, and respiratory system compliance, further supporting our study.

The study assessed respiratory rates, heart rates, and mean arterial pressures across two PEEP groups. For respiratory rates, group means were 18.98 ± 4.49 and 18.95 ± 5.25, showing no significant

difference [p=0.982]. Heart rates averaged 94.42 ± 25.4 and 92.95 ± 29.39 [p=0.811]. Mean arterial pressures were 79.8 ± 18.8 and 81.03 ± 19.45 , also not significantly different [p=0.775].

Aligning with our findings, **Algera et al.** [13] found no significant difference in respiratory rates between lower and higher PEEP strategies. Similarly, **Serpa Neto et al.** [3] reported no association between PEEP levels and any hemodynamic parameters across four RCTs.

Atelectasis is more common in patients with ARDS, especially with mandatory ventilation. While balancing atelectrauma and over-distension can be beneficial in ARDS patients, those without ARDS might not benefit as much from PEEP. A meta-analysis showed that higher PEEP is valuable mainly for severe ARDS, but there are few large RCTs for non-ARDS patients [10].

The study found no significant differences in developed complications, including ARDS [p=0.314], severe hypoxemia [p=0.775], and pneumothorax [p=0.556], between the two groups.

Our findings align with those of **Algera et al.** [13], who reported no statistically significant differences in the incidence of ARDS, VAP, pneumothorax, severe atelectasis, or in the use of vasopressors and sedatives between groups. The rates of severe hypoxemia were 20.6% versus 17.6%, and the need for rescue strategies was 19.7% versus 14.6% in the lower and higher PEEP groups, respectively.

In contrast, **Pettenuzzo et al.** [12] found that barotrauma, hypotension, and ventilation duration were comparable between the two groups. They did not observe any association between higher PEEP and clinical outcomes, apart from ARDS occurrence, but confirmed its link to physiological outcomes such as improved oxygenation.

In patients without ARDS, PEEP may not be the most significant factor in preventing VILI. Instead, driving pressure [DP] and mechanical power [MP] are considered key factors influencing injury. Lower DP and MP may benefit these patients, and tidal volumes [TVs] could better indicate VILI risk. Adjusting ventilation settings based on DP and MP might be more effective than focusing solely on PEEP [14].

In addition, the uncertainty of hospital mortality evidence is influenced by high bias in the analyzed studies, limiting our conclusions. Rigorous RCTs with well-defined patient populations are needed to assess the benefits of higher PEEP for non-

ARDS patients. Clinical heterogeneity among populations and outcomes also complicates the relationship between PEEP levels and clinical results [15].

Furthermore, certain non-ARDS patient subgroups may hypothetically benefit from higher PEEP, but the analyses did not identify any specific groups. Most studies selected PEEP arbitrarily rather than based on individual responses or lung recruitability. While higher PEEP can improve oxygenation by promoting alveolar recruitment, excessive levels may lead to complications like over-distension and reduced oxygen delivery. A ventilator titration strategy based on lung morphology could lower mortality in ARDS patients. However, data on driving pressure and compliance were limited, and trial analysis suggests further studies are unlikely to demonstrate a PEEP-mortality association, highlighting the need for revised patient selection criteria [16].

Ultimately, physiological benefits are more likely to lead to clinical improvements when initial physiological disturbances are significantly severe. However, for most patients, baseline oxygenation and compliance were reported to be nearly normal [17].

Contrary to our findings, **Serpa Neto et al.** [3]'s meta-analysis indicated that higher PEEP reduced ARDS and hypoxemia rates. However, there were no differences in pneumonia, atelectasis, barotrauma, or hypotension rates, and blood pressure was lower with higher PEEP.

The effectiveness of PEEP depends on lung recruitability, which is not fully understood. Both ARDS and non-ARDS patients may experience low lung recruitability, leading to complications such as alveolar over-distension and increased intrapulmonary shunt with high PEEP. Non-ARDS patients might benefit from lower tidal volumes in mechanical ventilation, but the overall impact of PEEP in this group remains uncertain [18].

In the study by **Yi et al.** [7] high PEEP was shown to reduce the incidence of ARDS and hypoxemia, which contradicts our findings.

Our results indicated no significant differences in mortality rates between the two studied groups across various time frames: ICU mortality [p=0.816], hospital mortality [p=0.82], 7-day mortality [p=0.82], and 28-day mortality [p=0.822]. Additionally, the groups did not differ significantly in ventilator-free days [p=0.056].

Our findings are consistent with those of **Algera *et al.*** ^[13], who reported no significant differences in median ICU and hospital lengths of stay, ICU and hospital mortality, or days free from ventilation between the groups. Similarly, **Serpa Neto *et al.*** ^[3] found no difference in in-hospital mortality between two PEEP arms across seven RCTs, nor in the duration of mechanical ventilation in three RCTs.

Pettenuzzo *et al.* ^[12] also reported no significant association between higher PEEP and hospital mortality [risk ratio 1.02; $p = 0.62$; low certainty of evidence]. Additionally, **Yi *et al.*** ^[7] found no significant differences in in-hospital mortality [RR 0.98; $P = 0.87$] or in the use of vasopressors or sedatives between high and low PEEP applications.

Our study contributes to the existing literature by showing that higher PEEP usage led to a decrease in driving pressure during the early days, consistent with findings from other meta-analyses involving patients with and without ARDS ^[3,19]. Additionally, we found no statistically significant differences in the use of vasopressors or sedatives, supporting the results of a previous study **Algera *et al.*** ^[13], which reported vasopressor use [$p = 0.47$] and sedation use [$p = 0.25$] as not significantly different.

While our study provides valuable insights into the effects of different levels of PEEP on non-ARDS patients, several limitations should be acknowledged. First, the sample size may limit the generalizability of our findings; a larger cohort would enhance the robustness and external validity of the results. Additionally, variations in clinical practice and protocols across different ICUs may influence the implementation of PEEP levels, leading to heterogeneity in treatment effects. Lastly, the short duration of monitoring might not capture the long-term implications of different PEEP levels on patient outcomes. Addressing these limitations in future research could provide deeper insights into optimizing PEEP in this patient population.

Conclusion: Ventilation with different levels of PEEP in ICU patients without ARDS at the onset of ventilation was associated with higher P_{O_2}/F_{iO_2} but not associated with decrease in ventilator free days nor lower in-hospital mortality nor a lower incidence of ARDS or pneumonia.

Financial Disclosures: None.

Conflict of Interest: None.

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IJMA



INTERNATIONAL JOURNAL OF MEDICAL ARTS

VOLUME 6, ISSUE 6, JUNE 2024

P- ISSN: 2636-4174
E- ISSN: 2682-3780